Although the proximal tubule of the kidney is known to express all of the above three types, it is widely accepted that Type II plays the most significant role in terms of phosphate reabsorption at this site. This has been demonstrated by a knockout mouse in which the gene (named Npt2) encoding Type II NaPi was inactivated. The homozygous mutants (Npt2-/-) exhibited increased urinary phosphate excretion, hypophosphatemia, elevation in the serum concentration of 1,25-dihydroxyvitamin D, and other typical symptoms with hereditary hypophosphatemic rickets with hypercalciuria (HHRH) (Beck, PNAS 95 (1998), 5372-5377). Since the regulation of phosphate homeostasis in mammals is largely determined by the kidney, this result is thought to demonstrate that Type II NaPi plays the most important role in systemic phosphate homeostasis among all three types. Also, these facts, together with the result from the CL8 cell line experiment in the examples indicate that the NaPi that is regulated by Phosphatonin in the kidney is predominantly the Type II.

One of the major clinical problems with renal failure patients is hyperphosphatemia. There is a significant clinical value if such excessive serum phosphate is controlled. Therefore, phosphatonin, its fragments or derivatives which can downregulate NaPi and reduce serum phosphate level has a major potential value. In progressive renal failure patients (before so-called end stage renal disease = ESRD), downregulation of NaPi expressing in the kidney by phosphatonin will be valuable.

However, once these patients become ESRD and the majority of kidney function is lost, phosphatonin will eventually lose its action site in the kidney because no more phosphate will be excreted from glomeruli. At such a disease stage, a potential value exists in controlling phosphate absorption from the diet in the digestive tract. The digestive tract, particularly the intestine, is the only place where phosphate is taken up from the diet into the circulation. Therefore, this will be the next major target to control phosphate uptake into the circulation after the kidney function is lost.

A subtype of the Type II NaPi, named Type IIb was reported to be cloned from mouse intestine (Hilfiker, PNAS 95 (1998), 14564-14569). Although it is yet to be known if phosphatonin can effect on the intestinal Type IIb NaPi, it is reasonably expected that this Type IIb NaPi in the intestine plays a major role in the absorption of phosphate from the diet and that phosphatonin may be the most significant factor for its up- and downregulation.

Example 7: Pharmaceutical Compositions

Pharmaceutical compositions may be formulated comprising a polypeptide according to the present invention optionally incorporating a pharmaceutically-acceptable excipient, diluent or carrier. The exact nature and quantities of the components of such compositions may be determined empirically and will depend in part upon the route of administration of the composition. Routes of administration to patients include oral, buccal, sublingual, topical (including ophthalmic), rectal, vaginal, nasal and parenteral (including intravenous, intraarterial, intramuscular, subcutaneous and intraarticular). In order to avoid unwanted proteolysis, a parenteral route is preferred.

Suitable dosages of a molecule of the present invention will vary, depending upon factors such as the disease or disorder to be treated, the route of administration and the age and weight of the individual to be treated. For instance for parenteral administration, a daily dosage of from 0.1μg to 1.5 mg/kg of a molecule of the invention may be suitable for treating a typical adult. More suitably the dose might be 1 μg to 150 μg. Accordingly, it is envisaged that the active polypeptide ingredient may be given in a dose range of from 0.01 to 100 mg, typically 0.1 to 10 mg, on a daily basis for an adult human.

Compositions for parenteral administration for example will usually comprise a solution of the molecule dissolved in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers can be used such as water, buffered water, 0.4% saline, 0.3% glycine etc. Such solutions should advantageously be sterile and generally free of aggregate and other particulate matter. The compositions may contain pharmaceutically acceptable buffers to adjust pH, or alter toxicity, for example sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, etc. The concentration of molecule in these formulations can vary

widely, for example from less than about 0.5% to as much as 15 or 20% by weight and could be selected as appropriate by a skilled person.

Typical pharmaceutical compositions are described in detail in Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pennsylvania (1980). For example, pharmaceutical compositions for injection could be made up to contain 1 ml sterile buffered water, and 50 mg of molecule. A typical composition for infusion could be made up to contain 250 ml of sterile Ringer's solution, and 150 mg of molecule. Actual methods for preparing compositions will be known or apparent to those skilled in the art. Approaches to formulation and administration of polypeptide pharmaceutical compositions are well-known to those skilled in this art and are discussed, for example, by P. Goddard in Advanced Drug Delivery Reviews, 6(1991) 103-131.

Example 8: Further characterization of phosphatonin (MEPE) and its encoding gene

Clinical profile of patients (BD, ND, EM and DS) with oncogenic osteomalacia:

Patient BD has been described in an earlier publication (Rowe, Bone 18 (1996), 159-169), and a case report for patient ND has also been published (David, J. Neurosug. 84 (1996), 288-292). Both patients exhibited classical tumour-osteomalacia, and presented with low serum phosphate and radiological osteomalacia, and low serum 1,25 vitam D_3. Patient BD (44 year old woman), and patient ND (66 year old woman), exhibited complete remission of symptoms after removal of tumours from the left nasal cavity (haemangiopericytoma), and the intracranial space (mesenchymal hemopericytoma like tumour), respectively. Patient ND had three such operations over a period of twenty years, and remission occurred after each resection.

Tumour conditioned media:

Tumour samples from both BD, ND and EM were collected immediately after resection. Samples were then cut into ~ 1 mm pieces and some frozen in liquid nitrogen. The remaining pieces of tumour tissue were processed for tissue culture as described previously (Rowe, Bone 18 (1996), 159-169). In brief, samples were digested with collagenase overnight, and then subjected to alternate cycles of